nivolumab, and pembrolizumab). The 2 terminated studies (both for idevaflib) were stopped owing to significant safety concerns. One product (ponatinib) was temporarily pulled from the market, with the FDA requiring further studies, and a risk evaluation and mitigation strategy; however, the PMR clinical study eventually resumed and was completed. One ongoing trial (for olaparib) was released as a PMR by the FDA. None of the pending or ongoing studies are behind their original schedules as posted in the FDA’s PMR database.

Discussion | Recently, the FDA has been criticized for its oversight of PMR clinical studies.2,3 The agency has come under fire for failure to penalize sponsors for PMR clinical studies completed late. Our own review of PMR clinical studies for novel oncology drug products granted AA within the last 6 years found that no studies were behind their original schedules. However, PMR studies identified serious safety concerns in 2 incidents that resulted in changes to the labeling for both products (idevaflib and ponatinib). In addition, our analysis identified 3 instances (20%) where confirmatory PMR clinical studies for drugs granted AA failed to meet their primary efficacy end points. To date, none of these 3 drugs have been pulled from the market. These examples underscore the importance of collecting the additional clinical safety and efficacy data outlined in the PMRs and the need for collaborative efforts between the FDA, sponsors, and investigators.

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The expected probabilities of each scenario with the drugs tisagenlecleucel and axicabtagene ciloleucel were calculated using input probabilities from the US Food and Drug Administration (FDA) Advisory Committee briefing document for tisagenlecleucel, the preliminary results of the Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-cell ALL (Acute Lymphoblastic Leukemia) (ELIANA) trial, and the FDA-approved label for axicabtagene ciloleucel. CRS indicates cytokine release syndrome.

### Table. Estimated Total Costs and Mean Expected Costs per Patient for Chimeric Antigen Receptor T-Cell Immunotherapies

<table>
<thead>
<tr>
<th>Treatment Scenario</th>
<th>Tisagenlecleucel</th>
<th>Axicabtagene Ciloleucel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base-Case Pricing</td>
<td>Outcomes-Based Pricing</td>
</tr>
<tr>
<td>Not treated</td>
<td>1207</td>
<td>1207</td>
</tr>
<tr>
<td>Treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>478 777</td>
<td>478 777</td>
</tr>
<tr>
<td>No response</td>
<td>478 777</td>
<td>377 253</td>
</tr>
<tr>
<td>Grade 1-2 CRS, received tocilizumab</td>
<td>502 464</td>
<td>502 464</td>
</tr>
<tr>
<td>Response</td>
<td>502 464</td>
<td>27 464</td>
</tr>
<tr>
<td>No response</td>
<td>502 464</td>
<td>27 464</td>
</tr>
<tr>
<td>Grade 1-2 CRS, received tocilizumab</td>
<td>504 276</td>
<td>29 276</td>
</tr>
<tr>
<td>Response</td>
<td>504 276</td>
<td>29 276</td>
</tr>
<tr>
<td>No response</td>
<td>504 276</td>
<td>29 276</td>
</tr>
<tr>
<td>Grade ≥3 CRS, received tocilizumab</td>
<td>530 011</td>
<td>55 010</td>
</tr>
<tr>
<td>Response</td>
<td>530 011</td>
<td>55 010</td>
</tr>
<tr>
<td>No response</td>
<td>530 011</td>
<td>55 010</td>
</tr>
<tr>
<td>Grade ≥3 CRS, received tocilizumab</td>
<td>531 823</td>
<td>56 823</td>
</tr>
<tr>
<td>Response</td>
<td>531 823</td>
<td>56 823</td>
</tr>
<tr>
<td>No response</td>
<td>531 823</td>
<td>56 823</td>
</tr>
<tr>
<td>Mean expected costs per patient treated</td>
<td>510 963</td>
<td>432 131</td>
</tr>
</tbody>
</table>

Abbreviation: CRS, cytokine release syndrome.

a All costs are expressed in 2017 US dollars.

b Under the outcomes-based pricing agreement announced by Novartis, the manufacturer of tisagenlecleucel, drug costs would be waived for those patients who do not respond to treatment within 1 month of administration.

c A CRS grade of 3 or greater represents severe CRS.

Discussion | To our knowledge, this study provides the first estimates of the total costs of CAR-T immunotherapy in the United States; these estimates are consistent with those previously calculated for the United Kingdom. Although our study did not examine the benefits associated with CAR-T immunotherapy and hence does not provide estimates of cost-effectiveness, it nevertheless has important implications.

One could argue that the nondrug costs associated with CAR-T immunotherapy are negligible when compared with drug costs, as the former represent 7% of total costs. However, in absolute terms, these nondrug costs are $30 000 to $36 000 for the average patient and as high as $56 000 for those
with severe CRS; these costs are equivalent to the costs of many of today’s most expensive medications. Moreover, under the proposed outcomes-based pricing arrangement, nondrug costs are not refunded for patients who do not demonstrate a response to treatment. Payers and the public must understand that only the costs borne by the manufacturer, but not the total costs of CAR-T immunotherapy, will be reimbursed for those who display no treatment response.

As the number of patients eligible for CAR-T immunotherapy and other expensive therapies increase, accurately measuring and accounting for the associated nondrug costs will be important when assessing the treatment’s true costs and value and when negotiating pricing arrangements.

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Assessment of Electronic Alert to Reduce Overuse of Granulocyte Colony-Stimulating Factor in Patients Hospitalized for Febrile Neutropenia

Prophylactic granulocyte colony-stimulating factors (G-CSFs) reduce the risk of febrile neutropenia (FN).1 Owing to the efficacy of prophylactic G-CSF, multiple studies have evaluated the therapeutic use of G-CSF during FN; however, no difference in overall mortality or infection-related mortality was observed.2 American Society of Clinical Oncology (ASCO) guidelines state that “G-CSFs should not be used for the treatment of FN. However, G-CSFs can be considered in patients at high-risk for complications.”3 Despite these guidelines, up to 62% of patients with FN receive G-CSF.3 Our objective was to evaluate the efficacy of an alert in the electronic health record (EHR) in reducing the therapeutic use of G-CSF.

Methods | This study was conducted from February 12, 2014, to April 12, 2016, at an academic multisite hospital where all orders are entered electronically. Beginning March 12, 2015, an EHR alert was triggered by the entry of an order for filgrastim or tbo-filgrastim. Clinicians were prompted to select an indication from a dropdown menu. If FN was selected, ASCO guidelines were displayed, and clinicians were required to select the indication.1 We compared the use of G-CSF the year prior to with the use of G-CSF the year after the alert was implemented. The study was approved by the Columbia University Medical Center and Weill Cornell Medical Center Institutional Review Boards, who waived patient consent, as the data were deidentified.

Patients were eligible if they had cancer and were hospitalized with FN. Covariates included age, sex, cancer type, and insurance. Patients were categorized as high risk if they were older than 65 years of age or had sepsis, pneumonia, or an invasive fungal infection. All analyses were conducted with SAS, version 9.4 software (SAS Institute Inc). P < .05 (2-sided) was considered significant.

Results | We identified 683 eligible patients, resulting in 880 unique admissions for FN (438 women and 442 men; mean [SD] age, 59.7 [15.8] years); 237 admissions (26.9%) were categorized as low risk (Table). There was no change in the use of G-CSF use before and after the alert (60 of 544 admissions [11.0%] vs 46 of 336 admissions [13.7%]; P = .62). Among the low-risk admissions, the use of G-CSF increased from 27 of 121 (22.3%) prior to the EHR alert to 40 of 116 (34.5%) after (P = .04) (Figure). Among the 643 high-risk admissions, the use of G-CSF did not change (139 of 423 [32.9%] vs 68 of 220 [30.9%]; P = .62). The most common indication selected was treatment of FN (44 of 108 admissions [40.7%]). However, prophylaxis was selected 20.4% of the time (22 of 108 admissions) (Table).

Discussion | We found that approximately one-third of patients hospitalized with FN received G-CSF, and the level of use did not decrease after the implementation of an EHR alert.